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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/568,572 | 08/14/2006 | Heidi Lopez de Diego | 453-US-PCT | 6471 |

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LUNDBECK RESEARCH USA, INC.
ATTENTION: STEPHEN G. KALINCHAK, LEGAL
215 COLLEGE ROAD
PARAMUS, NJ 07652

| EXAMINER | |
|---|---|
| BERNHARDT, EMILY B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 05/13/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/568,572 | DE DIEGO ET AL. | |
| | Examiner | Art Unit | |
| | EMILY BERNHARDT | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *47-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/16/06&6/26/06&1/31/07&8/1/07&10/9/07&2/12/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 49-53,55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
1.It is not seen how claims 49 and 55 further limit the cope of claims from which they respectively depend. There is no indication in the specification that amorphous forms of instant salts can be formed.
2. Claims 50-53 and 56-57 appear to be substantial duplicates within each set of claims as the only difference is the recitation of particular characterizing data or more complete X-ray powder diffraction peaks . Thus it is not seen how infringing one dependent claim would not also infringe remaining dependent claims within a given set.

Claims 54-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While being enabling for treating anxiety, depression, schizophrenia and psychotic disorders recited in claim 58, does not reasonably provide enablement for

treating remaining disorders or certain types of addiction particularly claimed in 60. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The notion that having combined affinity for the serotonin receptor (5-HT2A and D-1/D-2 receptors as well as α1 adrenoreceptors will enable treatment of all sleep, abuse disorders,migraine, any disorder exhibiting psychotic symptoms as well as neurolpetic-induced parkinsonism is not substantiated by the current state of the art. Note Robichaud at best describes treating depression and anxiety for 5-HT 2A antagonists and Zhang on p.590 discusses dopamine antagonists for treating psychoses, in particular, schizophrenia. Also see Gonzalez-Gomez article dealing with piperazine derivatives having a similar profile of activity as urged herein where the discussion is directed to use as anti-psychotics. Note also the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition which considers factors such as:

1) Breadth of the claims- The claims cover (but are not limited to) to all types of sleep disorders which include many, many different types even diametric opposites, eg. narcolepsy vs sleep apnea, any and all disorders

having psychotic symptoms which entails many different diseases of varying etiology, such as Alzheimer's Disease, Behcet's Disease, HIV-the latter for which it is known that anti-psychotic agents do not improve the psychotic symptoms. The scope of "abuse disorder" is not even a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine re-uptake site. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat chemical addictions generally have thus failed. While there are compounds undergoing preclinical and clinical trials for cocaine abuse that can block the behavioral effects of cocaine in animal models, there are no compounds that have proven efficacious in human cocaine addicts. See Newman, especially left column of p.1117 in the "Expert Opinion" section.

2) Level of skill in this art- as far as the examiner is aware drugs having the

profile of activity relied on herein are not known for such a spectrum of clinical applications and thus the level of skill is low ;

3) State of the prior art- compounds similar in structure (note Bogeso references applied below) have not demonstrated such a range of uses- only *in vitro* affinity towards various receptors as herein;

4) Working examples- There are no test(s) directed to the many uses pointed out above which are art-recognized for predicting *in vivo* efficacy in humans . Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of in vivo success for any additional diseases that may still be embraced in response to this action. See MPEP. 2164.05(a).

Thus in view of the above the rejection is being applied.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 47-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bogeso (J.Med. Chem) and Bogeso (EP'073) in view of Bogeso (US'448). The J. Med. Chem. article, teaches the instant trans isomer as the free base and in various salt forms for uses based on the same profile of activity as herein. See compound 38 in Table 5 which includes the racemate and (-) and (+) isomers as the maleate and fumarate salts. Applicants' claims appear to include the trans form as the racemate. There is otherwise no indication of a particular R/S configuration .The reference is devoid of a teaching directed to the particular salt forms claimed herein. EP Bogeso generically teaches compound 38 for the same uses claimed herein. See formula I on p.2 where R1 can be H or alkyl and Ar can be unsubstituted phenyl and 6-chloro can be present on the indan ring. Note Bogeso also includes the resolved isomers and particularly characterizes the invention as being directed to the trans- form. For a list of uses that overlap with that claimed herein, see p.3. Bogeso additionally teaches a variety of salt forms as suitable including those described by the J.Med. Chem. Article and also succinic acid one of the salt forms claimed herein See page 4.While malonic acid is not described, US'448 directed to similar compounds and uses teaches in addition to the many salt forms

taught by EP Bogeso additionally othet dicarboxylic acids, including malonic acid as described in col.32 therein. These are a list of preferred salts.

Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify compound 38 in Bogeso including the resolved forms by salifying the free base form or substituting one salt form for another that is well-known in the pharmaceutical art with the expectation that that such compounds will have the desired activity needed to practice the invention in view of the equivalency teachings outlined in EP Bogeso and US Bogeso.

The comparative showing in the specification on pages 34-35 have been noted but are not persuasive for more than one reason. The free base form was not tested against the instant salt forms nor was the maleate salt described in the Bogeso article. It is also noted that in all the examples the salt ratio is 1:1 yet the claims cover other proportions. Additionally, it has not been asserted that the differences while superior are unexpected. A recent decision directed to the patentability of a particular salt form of an old compound is pertinent to the instant fact situation. Note Pfizer v. Apotex 82 USPQ2d 1321 which despite having shown several superior

physiochemical properties for the besylate salt over the prior art salt, was held to be the result of “routine optimization that would have been obvious to one of ordinary skill in the art”.

Applicants’ IDS filed 2/21/08 has several duplicate entries which were crossed out. However, Cox is not seen in the file. A copy is needed for consideration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Bernhardt/
Primary Examiner, Art Unit 1624

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